I. AMENDMENT

Please make the following amendments:

In the claims:

Please amend claims 1, 9, 16, 24 and 75 as follows:

1. (Twice Amended) A method for detecting polymorphisms in a uridine diphosphate glucuronosyltransferase (UGT) gene promoter comprising determining the presence of five ~~or eight (TA)~~ (TA) repeats repeats in said promoter, wherein the presence of five TA repeats correlates with increased expression of the gene, ~~and the presence of eight repeats correlates with decreased expression of the gene.~~

8 9. (Twice Amended) A method for detecting polymorphisms in a uridine diphosphate glucuronosyltransferase I (UGT1A1) gene promoter comprising determining the presence of five (TA) or ~~eight (TA)~~ repeats in said promoter, wherein the presence of five TA repeats correlates with increased expression of the gene, ~~and the presence of eight repeats correlates with decreased~~ expression of the gene.

14 16. (Twice Amended) A method for screening individuals for variation in glucuronidation activity comprising detecting polymorphisms in a uridine diphosphate glucuronosyltransferase (UGT) gene promoter comprising determining the presence of five ~~or eight (TA)~~ (TA) repeats repeats in said promoter, wherein the presence of five TA repeats correlates with increased expression of the gene, ~~and the presence of eight repeats correlates with decreased expression of the gene.~~

21 24. (Twice Amended) A method for screening individuals for variation in glucuronidation activity comprising detecting polymorphisms in a uridine diphosphate glucuronosyltransferase I (UGT1A1) gene promoter, the method comprising determining the presence of five ~~or eight (TA) repeats~~ (TA) repeats in said promoter, wherein the presence of five TA repeats correlates with increased expression of the UGT gene, ~~and the presence of eight repeats~~ correlates with decreased ~~expression of the UGT gene.~~

B5 63 75. (Once Amended) The method of claim 27 ~~or 31~~ wherein the drug is TAS-103.

II. RESPONSE TO OFFICE ACTION

A. Claims in the case:

Claims 1, 16, 19, 24 and 75 have been amended. The currently pending claims include 1-6, 8-13, 15-21, 23-28, 30-62 and 70-75.

B. Rejection of Claims 1-30 and 70-75 Under 35 U.S.C. 112, 2nd Paragraph

The Action first rejects claims 1-30 and 70-75 under 35 U.S.C. 112, 2nd paragraph for various reasons discussed below.

First of all, claims 1, 9, 16, 24 were rejected, with the Action taking the position that the use of the word "or" rendered the claims indefinite in that, according to the Action, it was unclear whether the limitations following the phrase are part of the claimed invention.

In response, Applicants are unsure as to the basis of the rejection, and what limitations the Action is referring to as potentially not being a part of the claimed invention and how the word "or" might render the claim indefinite. It is, for example, intended that the invention of claim 1 be directed to the detection of either five or eight TA repeats in a UGT gene promoter. If such a promoter is screened and found to contain five TA repeats, such a screening would be covered by claim 1. Similarly, if such a promoter was screened and found to contain eight TA repeats, such a screening would be covered by claim 1. This is the essence of alternative claiming through the use of the word "or." In an attempt to try to address the Action's concerns, Applicants have amended the claims to insert the word "either" 5 "or" 8 in the hopes that this might be of some assistance in clarifying the underlying issue. Insertion of the word "or" is not in any way intended to change the scope of these claims, and is undertaken merely to try to

clarify what was intended by the previous amendments to the claims. Applicants would be pleased, however, to discuss this issue with the Examiner if the underlying basis of the rejection has been misunderstood.

The Action curiously refers to MPEP section 2173.05(d) in support of its rejection. However, this section of the MPEP refers only to the inappropriate use of language of preference in claims. This section deals with language like "for example" and "such as," which is clearly inappropriate. However, this is entirely different from the use of the "alternative claiming" word "or," which is specifically permitted under MPEP section 2173.05(h), subsection II.

With respect to claim 75, the typographical error has been corrected and the claim now refers to claims 31 and 39 in the same fashion as claim 74.

C. Rejection of Claims 1-30 and 70-75 over Beutler *et al.*

The Action first rejects claims 1-30 and 70-75 as anticipated under 35 U.S.C. § 102 (a) by Beutler *et al.* Applicants would again assert that the Beutler *et al.* publication is not available as prior art against the rejected claims. Applicants enclosed a further Declaration under Rule 131, demonstrating that the present inventors had discovered the existence and determined the relevance of both the 5 TA and 8 TA promoter prior to the publication date of the Beutler *et al.* publication. In the new declaration, the inventors point out that the data referred to in this Abstract was presented at the American Society for Clinical Pharmacology and Therapeutics meeting on March 30 - April 1, 1998 in New Orleans, Louisiana, and the Abstract reflecting this work was published prior to that time. Attached to the declaration is a copy of the slides that were presented (Exhibit B). As can be seen from the slides, the inventors fully presented a characterization of the allele 5 and allele 8, including a sequence analysis of each (see slide 6).

Furthermore, an analysis of the rate of bilirubin glucuronidation was carried out on the allele 5 and allele 8 carriers (see slide 7). From this study, the inventors demonstrated that carriers of allele 5 exhibited a bilirubin glucuronidation that was higher than that for the other genotypes, while the allele 8 carriers exhibited a glucuronidation level within the confidence levels of the allele 6 and allele 7 genotypes. Thus, this presentation demonstrates that the inventors had discovered the allele 5 and allele 8, and made an initial assessment of their biologic significance, prior to July, 1998.

It is submitted that this declaration, and the accompanying evidence submitted with the declaration, makes it clear that the Beutler *et al.* article is not available under Section 102(a).

D. Rejection of Claims on the Basis of Obviousness

The Action next rejects all of the pending claims over either Beutler *et al.* ("Beutler") in view of Clarke *et al.* ("Clarke"), taking the position that Beutler teaches the method of claims 1-30 and 70-73, respectively, and that Clarke teaches a method of screening individuals for variation in activity of glucuronidation of drugs and xenobiotics. The Action refers us to Section E, page 24-28, of Clarke in support of this position.

In response, Applicants again respectfully point out that the Beutler reference is not available under Section 102 (a) on the basis of the enclosed declaration. Most certainly, absent a specific teaching of a five or eight repeat promoter, and a teaching that such a promoter would have differences in terms of its promoter activity, there is no basis for arriving at a conclusion of obviousness with respect to any of the claims which specify this particular feature. This would include, at least, claims 1-30 and 70-71.

With respect to Clark, curiously, the Action makes no attempt whatsoever to address any of Applicants arguments presented in the previous response. As such, should an appeal be

necessary, Applicants hereby incorporate by reference the arguments presented in the previous response. Furthermore, Applicants again reiterate that that Clarke in no way teaches or suggests screening individuals for variation in activity of the glucuronidation of drugs and/or xenobiotics by looking for polymorphisms in the UDPGT promoter, nor does it teach a method for optimizing drug dosage or predicting an individual's sensitivity to drugs.

With respect to Clark, the Action first refers us to a statement at page 28, last four lines, for the proposition that Clark teaches that a method of identifying polymorphisms would prove to be of great benefit in modifying drugs so as to improve their pharmacokinetics. In response, Applicants would note that this section relates to the design of drugs that would otherwise be of little therapeutic value to improve their pharmacokinetics. As such, it is unclear specifically to what claim or claims the Examiner believes that this excerpt is relevant. In contrast, the pending claims here relate, for example, to a method of optimizing dosaging (claims 31 and 39) or a method of predicting a person's sensitivity to a drug (claim 55). Thus, the relevancy of Clark in this regard in still unclear.

The Action next takes the position that both Clark and Beutler make a connection between Gilbert's syndrome and dosage effects of acetaminophen to the UGT gene. In response, Applicants observe that Beutler is not available as prior art, and that Clark, on its face, states that there "have been no reports on the molecular basis of Gilbert's syndrome to date."

For the foregoing reasons, it is respectfully submitted that the prior art does not teach or suggest the invention embraced by any one of claims 1-62 or 70-73.

The Action further rejects the remaining claims, claims 74 and 75, on the basis of the foregoing references further in combination with Hausheer *et al.* ("Hausheer"), taking the position that Hausheer indicates that chemotherapeutic agents "possess primary cytotoxic